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Original article:

THE OBESITY PARADOX IS NOT OBSERVED IN CHRONIC HEART FAILURE PATIENTS WITH METABOLIC SYNDROME

Taro Narumi, Tetsu Watanabe*, Shinpei Kadowaki, Yoichiro Otaki, Yuki Honda, Satoshi Nishiyama, Hiroki Takahashi, Takanori Arimoto, Tetsuro Shishido, Takuya Miyamoto, Isao Kubota

Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, Yamagata, Japan

* Correspondencing author: Tetsu Watanabe, M.D.; Department of Cardiology, Pulmonology, and Nephrology; Yamagata University School of Medicine; 2-2-2 Iida-nishi, Yamagata, 990-9585, JapanPhone: +81-23-628-5302; Fax: +81-23-628-5305;
E-mail: tewatana@med.id.yamagata-u.ac.jp

ABSTRACT

Introduction: Although being overweight or obese is a risk factor for cardiovascular disease, obese subjects often live longer than their lean peers, and this is known as the obesity paradox. We investigated the impact of obesity on cardiac prognosis in chronic heart failure (CHF) patients, with or without metabolic syndrome.
Design and Methods: We divided 374 consecutive CHF patients into two groups according to their mean body mass index (BMI) and prospectively followed them for 2 years.
Results: There were 126 cardiac events, including 32 cardiac deaths and 94 re-hospitalizations. Kaplan-Meier analysis revealed a significantly lower cardiac event rate in the higher BMI group (log-rank test $P < 0.001$) in all patients and those patients without metabolic syndrome. There was no association between BMI and cardiac prognosis in patients with metabolic syndrome. Cox hazard analysis revealed that a higher BMI was associated with favorable cardiac outcomes in all patients and patients without metabolic syndrome, after adjusting for confounding factors. However, this finding did not extend to patients with metabolic syndrome.
Conclusions: The advantages of obesity are not found in CHF patients with metabolic syndrome.

Keywords: chronic heart failure, obesity paradox, metabolic syndrome, prognosis

INTRODUCTION

The increasing number of overweight or obese individuals in developed countries is linked to excessive calorie intake and reduced physical activity. Importantly, being overweight or obese is associated with the development of cardiovascular diseases, type II diabetes mellitus, stroke, respiratory problems, and psychological disorders (Dagenais et al., 2005; Wilson et al., 2002). Several cohort studies showed that a high body mass index (BMI) is associated with an increased risk for coronary artery disease, heart failure, and cardiac death (Calle et al., 1999; Dagenais et al., 2005). However, a number of studies reported that obese subjects often live longer than their lean peers, and this is termed the obesity paradox (Gastelurrutia et al., 2011; Horwich et al., 2001). Previously, obese patients with chronic heart failure (CHF) were found to have better prognoses compared with lean patients (Komukai et al., 2012). In contrast, the prevalence of cardiac

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cachexia increases with advancing CHF and is associated with poor prognosis (Anker and Sharma, 2002). However, it remains unclear whether obesity influences favorable outcomes in patients with CHF.

Increased abdominal visceral adipose tissues are able to produce adipocytokines, which induce chronic systemic inflammation (Libby et al., 2002). Chronic inflammation of visceral adipose tissue in turns raises insulin resistance, which is associated with sympathetic nerve activation and renin –angiotensin -aldosterone system activation in obese subjects (Patel and Abate, 2013; Shimizu et al., 2012). Therefore, we hypothesized that the presence of insulin resistance would negate any advantage of obesity in patients with CHF.

In the present study, we investigated the effect of obesity on cardiac prognosis in CHF patients with or without metabolic syndrome.

PATIENTS AND METHODS

Study population

Between September 2009 and October 2011, 469 consecutive patients were admitted to the Yamagata University Hospital for treatment of worsening CHF, for diagnosis and pathophysiological investigations, or for therapeutic evaluation of CHF. The diagnosis of CHF was based on a history of dyspnea and symptoms of exercise intolerance followed by pulmonary congestion, pleural effusion, or left ventricular enlargement by chest X-ray or echocardiography (Jessup et al., 2009; McKee et al., 1971). Five patients undergoing chronic hemodialysis and 14 patients with no weight or height information in their medical records were excluded. Forty-nine patients with no recorded serum albumin level were also excluded. The remaining 401 patients were prospectively followed (Figure 1). Informed consent was obtained from all patients before participation, and the protocol was approved by the institution's Human Investigation Committee. The procedures were performed in accordance with the Helsinki Declaration.

Definition of metabolic syndrome

We defined metabolic syndrome according to the National Cholesterol Education program Adult Treatment Panel III (NCEP-ATP III) criteria (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). We modified the NCEP-ATP III criteria for abdominal obesity by using a BMI $\geq$ 25 kg/m^2 instead of waist circumference (Hao et al., 2007). Metabolic syndrome requires at least three of the following five criteria:

- BMI $\geq$ 25 kg/m^2,
- elevated triglyceride $\geq$ 150 mg/dL,
- reduced high-density lipoprotein cholesterol $<$ 40 mg/dL in men and $<$ 50 mg/dL in women,
- elevated fasting blood sugar $\geq$ 110 mg/dL or previously diagnosed diabetes mellitus,
- elevated blood pressure (systolic blood pressure $\geq$ 130 mmHg, and/or diastolic blood pressure $\geq$ 85 mmHg), or antihypertensive medication use.

End points and follow-up

The patients were prospectively followed for 2 years. The end points were cardiac death, including death due to progressive CHF, myocardial infarction, stroke, other vascular causes, and sudden cardiac death, or re-hospitalization for worsening CHF. Sudden cardiac death was defined as death without definite premonitory symptoms or signs, and was confirmed by the attending physician. Two cardiologists, who were blinded to the blood biomarker data, reviewed the medical records and conducted telephone interviews to survey the incidence of cardiovascular events.

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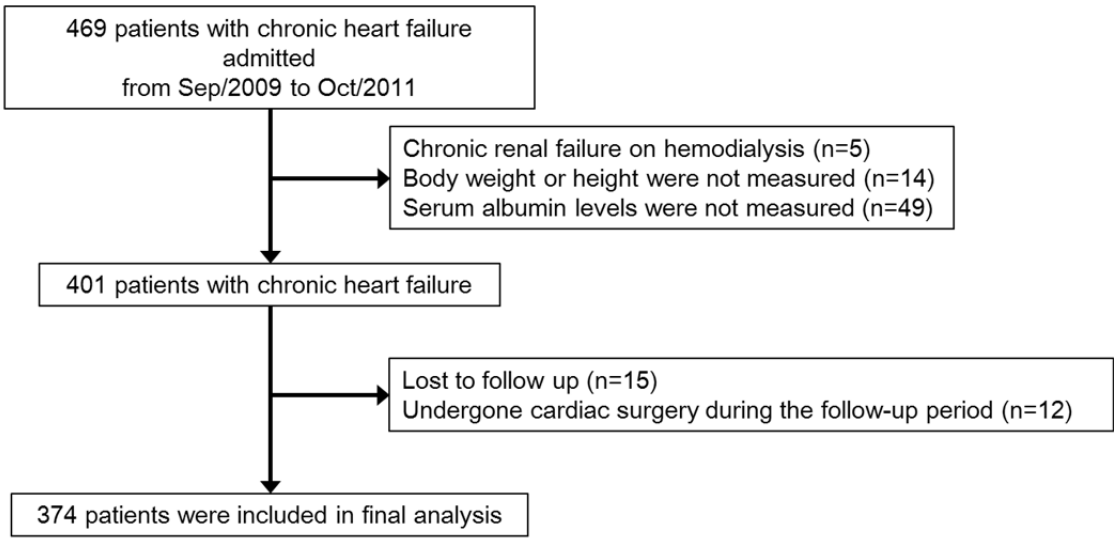

Figure 1: Recruitment of patients with chronic heart failure

Statistical analysis

Continuous data are expressed as means ± standard deviation (SD), and skewed data are presented as medians with interquartile range. The unpaired Student's t-test and chi-square test were used to compare continuous and categorical variables, respectively. The Mann-Whitney U-test was employed when the data were not normally distributed. A comparison of serum brain natriuretic peptide (BNP) levels and BMI tertiles was performed with Pearson's chi-square tests. Uni- and multivariate analyses with Cox proportional hazard regression were used to determine significant predictors of cardiovascular events. Multivariate analysis was adjusted by factors that were found to be significant in univariate analysis. Cumulative overall and event-free survival rates were computed using the Kaplan-Meier method and were compared using the log-rank test. A P value < 0.05 was considered statistically significant. All statistical analyses were performed with a standard statistical program package (JMP version 10; SAS Institute, Cary, North Carolina).

RESULTS

Patient characteristics

Twelve patients who underwent cardiac surgery during the follow-up period were excluded from analysis, and 15 patients were lost to follow-up. The remaining 374 patients were included in final analysis (Figure 1). Patient baseline characteristics are listed in Table 1. There were 223 males (60 %), and the mean age was 68 ± 12 years. There were 151 patients in New York Heart Association (NYHA) functional class III and IV. Heart failure etiology was identified as dilated cardiomyopathy in 102 (27 %) patients, valvular heart disease in 84 (23 %) patients, ischemic heart disease in 59 (16 %) patients, hypertensive heart disease in 44 (12 %) patients, hypertrophic cardiomyopathy in 19 (5 %) patients, and others in the remaining 66 (17 %) patients. Mean left ventricular ejection fraction as measured by echocardiography was 50 ± 17 %, and the median serum BNP level was 362 ng/L (interquartile range: 141.8-874.0).

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Comparison between patients with and without metabolic syndrome

There were 52 patients (14 %) with metabolic syndrome. They were younger and had higher BMIs compared with those without metabolic syndrome (Table 1). There were no significant differences in etiologies of CHF or medications.

Comparison between patients with and without cardiac events

There were 126 cardiac events (34 %), including 32 cardiac deaths and 94 re-hospitalizations, during the follow-up period (Table 2). The patients who experienced

Table 1: Baseline clinical characteristics and clinical characteristics of CHF patients with and without metabolic syndrome

	All Patients (n=374)	Non-MetS (n=322)	MetS (n=52)	*P* value
Age (years)	68 ± 12	70 ± 12	66 ± 13	0.011
Male, n (%)	223 (60)	189 (59)	34 (65)	0.361
NYHA functional class, II/III/IV	223/98/55	187/84/51	36/13/3	0.186
Etiology, n (%)				
Dilated cardiomyopathy	102 (27)	89 (28)	13 (25)	0.691
Valvular heart disease	84 (23)	76 (24)	8 (15)	0.187
Ischemic heart disease	59 (16)	49 (15)	10 (19)	0.461
Hypertensive heart disease	44 (12)	35 (11)	9 (17)	0.181
Hypertrophic cardiomyopathy	19 (5)	15 (5)	4 (8)	0.355
Others	66 (17)	58 (17)	11 (16)	0.784
Presentation profile				
Systolic pressure, mmHg	133 ± 15	135 ± 16	134 ± 15	0.659
Diastolic pressure, mmHg	78 ± 9	76 ± 10	75 ± 10	0.522
Body mass index, kg/m^2	22.2 ± 3.6	21.8 ± 3.3	25.1 ± 3.8	< 0.001
eGFR, ml/min/1.73m^2	62 ± 27	62 ± 25	62 ± 25	0.942
Blood biomarkers				
Total protein, g/dl	6.5 ± 0.7	6.5 ± 0.7	6.6 ± 0.5	0.095
Albumin, g/dl	3.6 ± 1.9	3.6 ± 2.0	3.7 ± 0.6	0.756
Total cholesterol, mg/dl	173 ± 41	135 ± 16	160 ± 76	0.869
Triglyceride, mg/dl	98 ± 57	92 ± 50	139 ± 50	< 0.001
LDLc, mg/dl	99 ± 32	98 ± 30	108 ± 39	0.039
HDLc, mg/dl	53 ± 20	50 ± 17	43 ± 14	< 0.001
BNP, pg/ml (IQR)	362 (142-874)	377 (152-905)	197 (72-848)	0.273
Echocardiographic data				
LV end-diastolic diameter, mm	55 ± 10	55 ± 10	57 ± 9	0.108
LV ejection fraction, %	50 ± 17	50 ± 17	51 ± 18	0.883
Medications, n (%)				
ACE inhibitors and/or ARBs	263 (70)	228 (71)	35 (67)	0.608
β blockers	188 (50)	166 (52)	22 (42)	0.216
Ca channel blockers	84 (23)	70 (22)	14 (27)	0.405
Statins	90 (24)	77 (24)	13 (25)	0.864

Data are presented as mean ± SD or % unless otherwise indicated; IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HDLc, high density lipoprotein cholesterol; LDLc, low density lipoprotein cholesterol; LV, left ventricular; MetS, metabolic syndrome; NYHA, New York Heart Association

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Table 2: Clinical characteristics of CHF patients with and without cardiac events

	Event (-) (n=248)	Event (+) (n=126)	*P* value
Age (years)	68 ± 12	72 ± 11	0.007
Male, n (%)	141 (57)	34 (61)	0.125
NYHA functional class, II/III/IV	166/52/30	57/45/24	<0.001
Etiology, n (%)			
Dilated cardiomyopathy	61 (25)	41 (33)	0.103
Valvular heart disease	61 (25)	23 (18)	0.164
Ischemic heart disease	35 (14)	24 (19)	0.215
Hypertensive heart disease	33 (13)	11 (9)	0.194
Hypertrophic cardiomyopathy	14 (6)	5 (4)	0.485
Others	44 (17)	22 (17)	0.899
Presentation profile			
Systolic pressure, mmHg	134 ± 15	134 ± 16	0.621
Diastolic pressure, mmHg	79 ± 10	79 ± 9	0.428
Body mass index, kg/m^2	22.6 ± 3.6	21.5 ± 3.4	0.002
eGFR, $ml/min/1.73m^2$	63 ± 29	60 ± 21	0.294
Blood biomarkers			
Total protein, g/dl	6.6 ± 0.7	6.4 ± 0.8	0.019
Albumin, g/dl	3.9 ± 2.2	3.1 ± 0.8	<0.001
Total cholesterol, mg/dl	178 ± 39	165 ± 46	0.008
Triglyceride, mg/dl	104 ± 62	87 ± 44	0.008
LDLc, mg/dl	101 ± 32	96 ± 32	0.192
HDLc, mg/dl	54 ± 22	50 ± 16	0.037
BNP, pg/ml (IQR)	583 (123-661)	853 (220-1230)	0.041
Echocardiographic data			
LV end-diastolic diameter, mm	55 ± 10	56 ± 10	0.102
LV ejection fraction, %	52 ± 17	47 ± 17	0.003
Medications, n (%)			
ACE inhibitors and/or ARBs	169 (68)	94 (75)	0.196
β blockers	116 (47)	72 (57)	0.058
Ca channel blockers	50 (20)	34 (27)	0.059
Statins	52 (21)	38 (31)	0.135

Data are presented as mean ± SD or % unless otherwise indicated; IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HDLc, high density lipoprotein cholesterol; LDLc, low density lipoprotein cholesterol; LV, left ventricular; NYHA, New York Heart Association

cardiac events were older, in a more severe NYHA functional class, and showed lower BMI and left ventricular ejection fraction compared with those who did not. Moreover, patients with cardiac events showed lower serum levels of total protein, albumin, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and higher serum BNP levels compared with those who did not experience events. There were no significant differences in etiologies of CHF or medications between patients with and without cardiac events.

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Association between BMI and serum BNP levels

The patients were divided into two groups according to their mean BMI (lower G1 and higher G2), respectively. In all CHF patients, and those without metabolic syndrome, serum BNP levels were higher in lower serum BMI groups than in higher serum BMI groups (both $P < 0.001$; Figure 2A, B). However, there was no association between BMI and serum BNP levels in patients with metabolic syndrome ($P = 0.207$, Figure 2C).

Association between BMI and cardiac events

In univariate Cox hazard analysis, the unadjusted hazard ratio (HR) for cardiac events was significantly decreased with increasing BMI in all patients (G2: unadjusted HR 0.48, 95 % confidence interval (CI) 0.33-0.69) and patients without metabolic syndrome (G2: unadjusted HR 0.45, 95 % CI 0.30-0.67) but not in those with metabolic syndrome (G2: unadjusted HR 1.81, 95 % CI 0.70-4.62) (Table 3). Multivariate analysis revealed that a higher BMI was associated with the lower risk in all patients and those without metabolic syndrome after adjustments for age, gender, NYHA functional class, and serum BNP levels (adjusted HR 0.55, 95 % CI 0.38-0.79; adjusted HR 0.52, 95 % CI 0.35-0.79; respectively). Kaplan-Meier analysis revealed that significantly lower cardiac event rates were observed in higher BMI (G2) in both CHF patients and patients without metabolic syndrome (log-rank test, both $P < 0.001$; Figure 3A, B). Meanwhile, there was no significant association between BMI and cardiac events in patients with metabolic syndrome (log-rank test $P = 0.220$, Figure 3C).

DISCUSSION

The present study has demonstrated that obese patients with CHF had a better cardiac prognosis than lean patients, consistent with previous reports (Horwich et al., 2001; Komukai et al., 2012). However, favorable cardiac outcomes were not observed in obese patients with metabolic syndrome.

Although being overweight or obese is a well-recognized independent risk factor for cardiovascular diseases, a large number of cohort studies have shown that obesity is not necessarily associated with increased mortality in patients with CHF, but can be associated with a favorable prognosis in patients with CHF (Gastelurrutia et al., 2011; Kenchaiah et al., 2007). The present study also demonstrated that obese patients with

Table 3: Unadjusted and adjusted hazard ratio for factors predicting cardiovascular events in heart failure patients with and without metabolic syndrome

	Unadjusted HR	95 % CI	P value	Adjusted HR	95 % CI	P value
All patients						
G1	1	Reference	Reference			
G2	0.48	0.33-0.69	<0.001	0.55	0.38-0.79	0.001
Non-MetS patients						
G1	1	Reference	Reference			
G2	0.45	0.31-0.67	<0.001	0.52	0.35-0.79	0.002
MetS patients						
G1	1	Reference	Reference			
G2	1.81	0.70-4.62	0.219	-	-	-

CI, confidence interval; HR, hazard ratio; MetS, metabolic syndrome. Adjusted HR, after adjustment of age, gender, New York Heart Association functional class, and serum levels of brain natriuretic peptide

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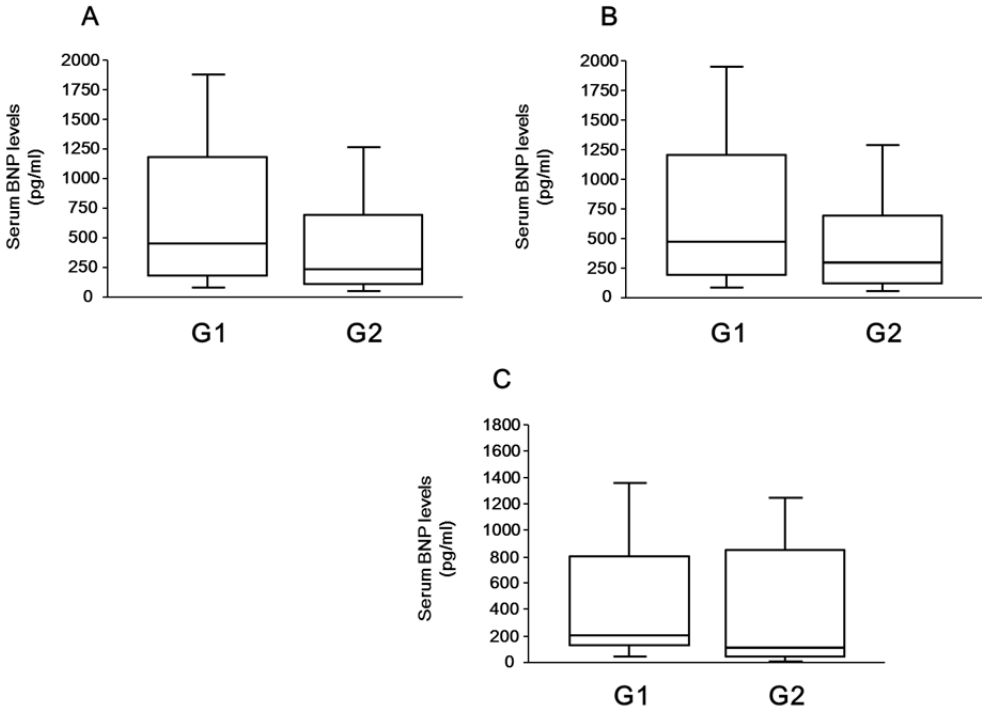

Figure 2: The association between BMI and serum BNP level. **A:** In all CHF patients, serum BNP levels decreased with increasing BMI ($P < 0.001$). **B:** In patients without metabolic syndrome, serum BNP levels also decreased with increasing BMI ($P < 0.001$). **C:** There was no association between BMI and serum BNP levels in patients with metabolic syndrome ($P = 0.207$). (BMI, body mass index; BNP, brain natriuretic peptide; CHF, chronic heart failure)

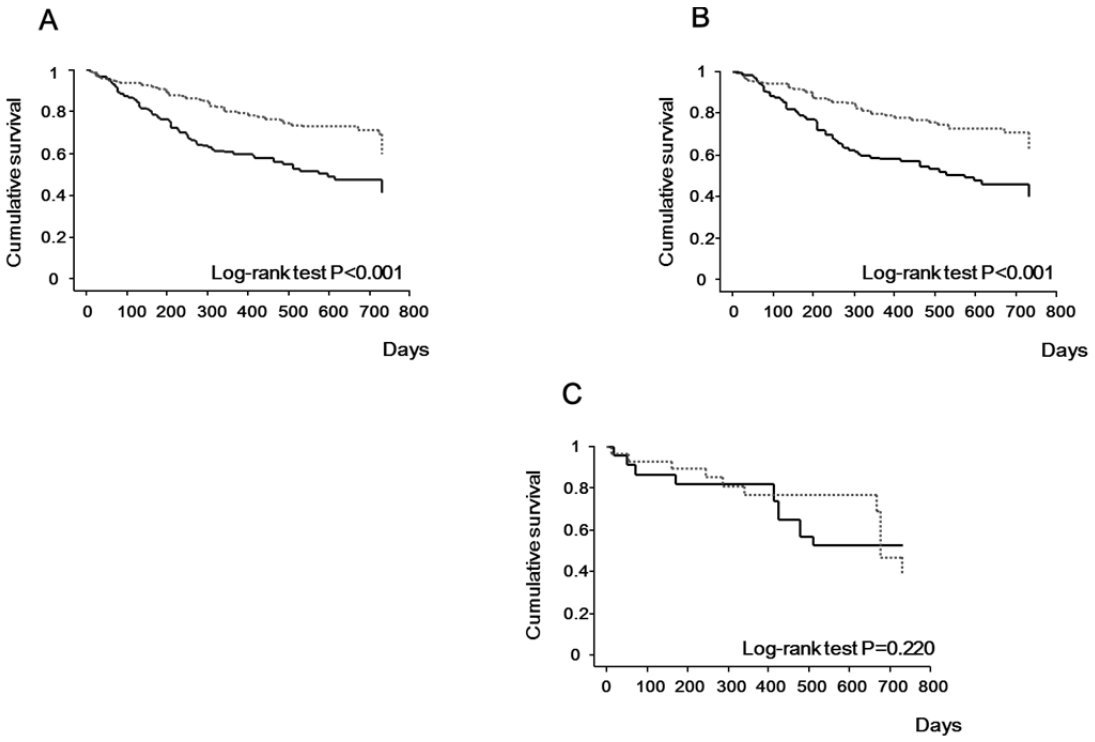

Figure 3: Kaplan-Meier analysis **A:** Significantly lower cardiac event rates were observed in higher BMI (G2) in all CHF patients (log-rank test, $P < 0.001$). **B:** Significantly lower cardiac event rates were also observed in higher BMI (G2) in CHF patients without metabolic syndrome (log-rank test, $P < 0.001$). **C:** A survival rate did not have significant difference between two groups (log-rank test, $P = 0.220$). (BMI, body mass index; CHF, chronic heart failure)

CHF have a better cardiac prognosis than lean patients. However, the pathophysiological mechanism of the obesity paradox remains unclear. Curtis et al. hypothesized that because cardiac output and myocardial demands are increased in obese patients, heart failure may be diagnosed earlier than in lean patients (Curtis et al., 2005). Komukai et al. (2012) also hypothesized that CHF is a catabolic state and because obese patients have greater metabolic reserve, obese patients may have better prognoses. Kistorp et al. (2005) reported that high levels of adiponectin, which is a well-known adipocyte-specific cytokine that is decreased in obesity, are associated with an increased risk of mortality in patients with CHF.

However the prevalence of cardiac cachexia is increased with worsening CHF, which is associated with a poor prognosis in patients with advanced CHF (Anker and Sharma, 2002). Anker et al. (1997) reported that the prevalence of cardiac cachexia was 42 % in CHF outpatients, and patients with cardiac cachexia showed 50 % mortality at 18 -months, which is comparable or higher than that in patients with malignant tumors. It was reported that several inflammatory cytokines, such as interleukin 1, interleukin 6, and tumor necrosis factor alpha, are elevated in patients with CHF, and induce chronic inflammation and metabolic disorder due to insulin resistance (Berry and Clark, 2000; Levine et al., 1990). These immune and neurohormonal abnormalities may contribute to the development of cardiac cachexia and a poorer cardiac prognosis.

Several studies reported that obese patients with additional risk factors (e.g., metabolic syndrome) are at a substantially higher risk of developing cardiovascular disease (Echahidi et al., 2007; Kajimoto et al., 2009). Nakamura et al. (2001) found that patients with metabolic syndrome were at a 31.3–fold greater risk of cardiovascular disease compared to those without. Shimizu et al. (2012) reported that chronic pressure overload in patients with CHF raises insulin resistance, which leads to metabolic syndrome. Individuals with metabolic syndrome produce various cytokines and develop a catabolic state due to chronic adipose tissue inflammation and insulin resistance (Ashrafian et al., 2007). Because insulin resistance is associated with sympathetic nerve activation and renin – angiotensin -aldosterone system activation (Shimizu et al., 2012), favorable cardiac outcomes are not observed in obese patients with metabolic syndrome. The presence of insulin resistance may negate the advantages previously described in obese patients with CHF. However, further investigation is required to elucidate the mechanism by which metabolic syndrome results in a poorer cardiac prognosis in obese patients with CHF.

There were several limitations in the present study. First, the number of CHF patients with metabolic syndrome was small in the present study. The prevalence of metabolic syndrome was reported to be 7-20 % in the general population and 20-40 % in patients with CHF in Japan (Hao et al., 2007; Miura et al., 2010). Our results corresponded with these reports. Although statistical analysis was possible for CHF patients with metabolic syndrome, future study will need to clarify the association between obesity paradox and CHF patients with metabolic syndrome in large population. Second, because data regarding waist circumference were not available, we modified the NCEP-ATP III criteria for abdominal obesity and used a BMI $\geq$ 25 kg/m^2 (Hao et al., 2007). Third, the BMI distribution of our study patients was lower than that reported in studies carried out in European countries and in the United States (Gastelurrutia et al., 2011). Therefore, we defined obesity as a BMI $\geq$ 25 kg/m^2 by using Japanese criteria (Examination Committee of Criteria for 'Obesity Disease' in Japan, 2002).

In conclusion, favorable cardiac outcomes were observed in obese CHF patients without metabolic syndrome. However, there was no favorable impact of obesity on clinical outcomes in CHF patients with metabolic syndrome.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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